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EFFECTS OF METHOTREXATE ON THE LIVER IN PSORIASIS*

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ABSTRACT

Seventy patients with psoriasis severe enough to require methotrexate therapy were evaluated to assess the effects of the drug on both liver function and histology. Thirty-five patients had not received methotrexate (untreated) and 35 patients had previously received methotrexate (treated). A total of 102 liver biopsies were performed in these 70 patients. A review of the liver biopsy specimens showed no statistically significant differences in the histologic changes between the treated and untreated patients. The lack of reliable correlation between the liver function tests and the histologic findings noted in previous studies was confirmed in this study.

In the 35 untreated patients, nondiagnostic changes were seen in the liver biopsies of 28 patients (80%) and significant fibrosis in only 1 patient (3%). No biopsy showed cirrhosis. In the 35 treated patients, nondiagnostic changes were seen in 25 patients (71%), significant fibrosis in 2 patients (6%), and cirrhosis in 1 patient (3%). Thirty-two repeat biopsies in 21 patients showed no progression in the fibrosis scores up to a period of 27 months of therapy, thus raising doubts about the necessity of performing routine liver biopsies in those patients receiving methotrexate on an intermittent regimen.

The reports of significant liver damage following methotrexate therapy for psoriasis have resulted in a reevaluation of the use of methotrexate for this disease. Following the report by Coe and Bull in 1968 [1] of postnecrotic cirrhosis, presumably related to methotrexate therapy for psoriasis, a comprehensive study was undertaken at Washington University Medical Center to evaluate both liver function and histologic changes in liver specimens obtained by needle biopsy in those patients requiring methotrexate to control their psoriasis. In this report we present our experience with 70 patients in whom a total of 102 liver biopsies were performed from 1969 to 1973.

During this time period additional cases of cirrhosis [2–6] as well as efforts to evaluate the effect of methotrexate on the liver [7–13] have been reported, and the National Program for Dermatology has established guidelines [14] for the use of methotrexate which include a reasonable approach to the problem of hepatotoxicity. Recently the preliminary results of an international cooperative study were published which included the evaluation of 742 liver biopsy specimens [15].

Our data are presented to add further information concerning the effects of psoriasis and methotrexate on the liver. The interpretation of the data has led us to question the necessity for performing a routine liver biopsy when methotrexate is used on an intermittent regimen for the treatment of psoriasis.

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PATIENTS AND METHODS

Seventy patients with psoriasis considered severe enough to require methotrexate were studied. Thirty-five patients had not received methotrexate previously (untreated); the other 35 had received methotrexate (treated) prior to inclusion in this study. Hepatic evaluation included a liver biopsy, serum alkaline phosphatase, SGOT, SGPT, bilirubin, and a BSP (normal, less than 5% retention at 45 min). Our protocol required the discontinuation of the methotrexate if significant histologic abnormalities were seen on liver biopsy. Patients continuing to receive methotrexate were restudied at intervals of approximately 6–12 months. From the time of the initial liver biopsy, patients received further methotrexate in only single intermittent (intramuscular or oral) but moderately high doses (25–50 mg) as opposed to a continuous daily low-dose regimen with rest periods. In a few cases the divided dose, intermittent oral schedule over a 36-hr period [16] was used.

Alcohol History

We assumed that alcohol intake might be one of the most important factors in the development of significant hepatic damage. Alcohol consumption was arbitrarily divided into two groups: (1) no alcohol to minimal alcohol ingestion (1–2 ounces of hard liquor per week or its beer equivalent), and (2) moderate to excessive alcohol ingestion (regular daily intake of hard liquor or beer or sporadic heavy use of either). Following the initial liver biopsy, patients were asked to abstain completely from alcohol and were warned that any alcohol intake might lead to permanent liver damage.

Liver Biopsies

All liver biopsies were performed by the Gastroenterology Division using the Menghini 1-sec technique [17] with a 16-gauge aspiration needle. Slides were routinely stained with hematoxylin and eosin. Stains for connective tissue (Masson's trichrome) were performed when indicated by the review of the hematoxylin and eosin stained tissues.

Sections of all 102 liver biopsies were reviewed by four observers, three surgical pathologists and one gastroenterologist (R.A.), in two sittings in a random blind fashion. The coded sections from those patients with more than one biopsy were recoded and evaluated a second time. Sections were graded on a 0 to 4 scale by each reviewer as outlined in Table I. The four individual scores were added and the sum total used in the multivariate analysis of data. A biopsy was considered to be normal only if the score in all categories was 0.

The histologic parameter was given a score of 0 unless two or more of the four observers indicated at least a grade 1 abnormality with the sum of the four observers being at least 3. Detectable abnormalities in any histologic parameter given a total score of less than 8 by the four observers (with an average score of less than 2) were considered to be nondiagnostic changes. A significant abnormality was arbitrarily defined for any histologic parameter in which the sum of the four observers was equal to or greater than 8 (with an average score of 2 or more).

Statistical Analysis

The 70 patients were ranked (with grouping) according to the total score (range 0–16) for each of five histologic parameters (hyperploid nuclei, fat, inflammation, fibrosis, and necrosis) and the ranks transformed into standard normal scores. Only the initial biopsy of each patient was used in the statistical evaluation. Multivariate analysis of variance [18] was employed to test the effects of alcohol (no to minimal alcohol ingestion vs. moderate to excess alcohol ingestion) and methotrexate (no previous methotrexate therapy vs. previous methotrexate therapy). The effect of schedule (continuous vs. intermittent methotrexate administration) within the methotrexate-treated group was analyzed separately by a multivariate analysis of covariance in order to facilitate adjustment for the dose (in logarithms of the total dose)

TABLE I

Grading of histologic changes in liver biopsies

Histologic parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyperploid nuclei	Majority of nuclei of same diameter with a few smaller and a few larger (i.e., 3 sizes)	Wide diversity in range of nuclear sizes (i.e., more than 3 distinct sizes) with small nuclei still predominating	As grade 1 but with smallest nuclei in minority	Most nuclei at least 3 times the diameter of smallest	Numerous very large bizarre nuclei
Fat	None	Less than 5% of hepatocytes involved	5–15% of hepatocytes involved	15–30% of hepatocytes involved	More than 30% of hepatocytes involved
Inflammation	Less than 10–20 lymphocytes/ portal tract. None in lobule	Average of 20–200 lymphocytes/ portal tract. Rare foci of 1–3 cells in lobule	Average of 200–1000 lymphocytes/portal tract. 1–3 foci/ lobule with 3–10 cells	More than 1000 lymphocytes/ portal tract and/or occasional polys or eosinophiles. More than 3 foci/lobule with more than 10 cells	Confluent innumerable cells in portal tract containing a mixture of cells or predominantly of PMNL'S. Widely dispersed or confluent areas of inflammation
Fibrosis	None	Perceptible increase in fibrous connective tissue in portal or central areas	Stellate fibrosis around centrolobular veins or increase in portal connective tissue not sufficient to connect adjacent landmarks	Portal or centrolobular fibrosis of such extent as to connect (or bridge) adjacent portal or central areas but not uniformly	Uniform fibrosis, connective tissue bands connecting portal and central areas, cutting parenchyma into nodules
Necrosis-degeneration	None	At least 1 cell seen in some stage of degeneration	1–3 degenerating cells/lobule	5–10 degenerating cells/lobule	15–20 degenerating cells/lobule or more (up to large confluent areas or foci.)

and duration of therapy (in logarithms of actual duration of therapy).

RESULTS

No Previous Methotrexate Therapy (Untreated) and No to Minimal Alcohol Intake

Seventeen patients were included in this group. Five patients (29.5%) had normal liver biopsy specimens by the definition of "normal" discussed above. Nondiagnostic changes were observed in the remaining 12 cases (70.5%) including mild perceptible fibrosis in 1 patient (5.9%) (case #9). The BSP was abnormal in 7 of the 16 patients in whom it was performed (43.8%). In all 7, the values were less than or equal to 8.0% of the administration dose of BSP at 45 min. The results in this group are shown in Table II.

No Previous Methotrexate Therapy (Untreated) and Moderate to Excessive Alcohol Intake

This group consisted of 18 patients. Only 1 patient had a normal liver biopsy specimen. Nondiagnostic changes were seen in 16 of the remaining patients (88.8%) including mild detectable fibrosis in 7 (38.9%). Significant fibrosis was seen in only 1 patient (5.6%) (case #25). The BSP was abnormal in 8 (50.0%) of the 16 patients in whom it was performed. The results in this group are shown in Table III.

Previous Methotrexate Therapy (Treated) and No to Minimal Alcohol Intake

Sixteen patients were included in this group. Six patients (37.5%) had a normal liver biopsy specimen. Eight patients (50.0%) showed nondiagnostic histologic changes including mild detectable fibrosis in 3 (18.8%). Significant fibrosis was seen in 1 patient (6.3%) (case #37) and 1 patient had frank cirrhosis (6.3%) (case #41). The BSP was abnormal in 5 of the 13 patients in whom it was performed (38.6%). The results in this group are shown in Table IV.

TABLE II

Grading of liver biopsies in patients with no previous methotrexate therapy and no to minimal alcohol intake

Case	Age at biopsy	BSP	Hyperploid nuclei	Fat	Inflammation	Fibrosis	Necrosis
1	55	1.6	4	3	1	0	0
2	22	5.8	0	0	1	0	0
3	31	2.9	1	0	5	0	0
4	53	6.6	3	1	4	0	0
5	18	5.4	2	0	3	1	0
6	28	6.7	3	4	1	0	0
7	21	2.2	2	0	5	1	0
8	43	8.0	0	0	2	2	0
9	34	7.8	1	1	3	3	0
10	40	2.4	0	0	0	0	0
11	36	1.4	1	9	0	0	0
12	48	2.4	0	0	1	0	0
13	48	1.1	1	0	1	0	0
14	59	2.3	1	6	3	0	0
15	74	5.7	6	3	3	0	0
16	22	3.3	0	5	0	0	1
17	58	n.d.*	2	4	5	1	0

* n.d. = not done

TABLE III

Grading of liver biopsies in patients with no previous methotrexate therapy and moderate to excessive alcohol intake

Case	Age at biopsy	BSP	Hyperploid nuclei	Fat	Inflammation	Fibrosis	Necrosis
18	45	28.7	3	9	6	6	1
19	24	2.9	0	0	0	0	0
20	55	2.3	2	1	3	1	1
21	46	7.4	1	9	2	1	0
22	46	18.6	3	10	5	5	1
23	40	4.3	0	9	1	0	0
24	48	4.1	5	0	0	0	0
25	59	5.0	3	10	8	9	2
26	38	5.2	5	10	2	1	1
27	59	10.1	0	4	5	6	1
28	28	2.5	1	0	6	2	0
29	39	4.4	3	9	4	2	1
30	42	n.d.*	1	4	3	3	0
31	55	5.2	1	4	0	0	0
32	48	7.5	2	8	3	3	0
33	38	n.d.	1	4	0	3	0
34	54	3.3	3	9	6	4	1
35	47	6.5	0	4	3	3	0

* n.d. = not done

The one patient in our series with cirrhosis (case #41) is a 57-year-old male who had increasingly severe psoriasis since age 23. He was placed on daily low-dose oral methotrexate by his local physician in September 1967 with weekly rest periods of several days. This regimen was continued for approximately 2.5 years, when elevated liver function tests were first detected. The patient was hospitalized elsewhere in March 1970 and found to have abnormal liver enzymes, hepatomegaly, and a serum bilirubin of 2.8 mg%. Methotrexate was discontinued. In July 1970 the patient was placed on Orinase for diabetes. There was no history of any alcohol ingestion. The patient was hospitalized at Barnes Hospital in September 1970 for treatment of his psoriasis. A liver biopsy was interpreted as active focal necrosis with collapse (scarring). BSP retention was 12.9% at 45 min. The patient was not considered a candidate for further methotrexate therapy and has since been treated with tar and ultraviolet light. A repeat BSP in October 1972 was 18.5%.

Previous Methotrexate Therapy (Treated) and Moderate to Excessive Alcohol Intake

This group consisted of 19 patients. Only 1 patient (5.3%) had a normal liver biopsy specimen. Seventeen patients (89.4%) had only nondiagnostic changes which included mild detectable fibrosis in 6 patients (31.6%) and significant fibrosis in 1 instance (5.3%) (case #68). No cirrhosis was seen. The BSP was abnormal in 6 out of 14 patients in

whom it was performed (42.9%). The results in this group are shown in Table V. It should be emphasized that patients who may have previously been informed of the potential role of alcohol in inducing hepatic abnormalities might tend to falsify their history in the hope of obtaining methotrexate. In one case (#70) the liver biopsy was histologically consistent with acute alcoholic hepatitis in spite of the patient's denial of any alcohol intake.

Follow-up Biopsies

Twenty-one patients were rebiopsied at least one time for a total of 32 repeat biopsies. The interval between biopsies was from 6–27 months (average = 12.4 months). No additional methotrexate was given between the first and second liver biopsies in 3 patients (cases #66, 68, 69) because of fear of significant liver damage. In retrospect the original biopsies in these 3 patients did not justify withholding methotrexate, and methotrexate was resumed in 2 of the 3 cases. The average dose of methotrexate between biopsies in the remaining 28 biopsies was 823 mg. No patient showed any progression in the fibrosis score in this group of follow-up biopsies.

A complication of liver biopsy occurred in 1 patient who developed an insidious bleed post-biopsy eventually requiring a laparotomy. The patient's recovery from surgery was uneventful.

In only 2 cases, #18 and #41, were the bilirubin and liver enzyme values abnormal. Case #18, an alcoholic, was not placed on methotrexate. Case #41 was the only patient in this series with cirrhosis.

The results of the multivariate analysis show no statistically significant ($p = 0.4$) effect of methotrexate treatment (vs. untreated) in the liver biopsy specimens. On the other hand, there is a statistically significant ($p < 0.001$) effect of alcohol intake on the histology of the biopsy specimens. This difference is attributable largely to the fat score and to a lesser extent the fibrosis score. However, when analyzed separately, the combination of moderate to excess alcohol plus previous methotrexate therapy did not show a significantly greater tendency toward fat or fibrosis than the other groupings.

The results of the analysis for the schedule of administration of methotrexate after adjusting for dose and duration of therapy are only suggestive ($p = 0.02$) of the possibility that continuous therapy at any given total dose and therapy duration, results in more hyperploid nuclei and to some extent fibrosis. This is in contrast to the intermittent regimen in which there is no evidence of hepatic damage. In the analyses of the schedule of administration we were able to compare the two regimens in only 31 of 35 patients because of insufficient data in 2 patients and a combination of regimens in 2 others.

DISCUSSION

The present report outlines the Washington University Medical Center's experience on the effects of methotrexate on the liver in 70 patients with psoriasis requiring methotrexate for control of the disease. Based on the results of the analysis of the data obtained from 102 liver biopsies, the decision was made to stop the study, especially its prospective nature. A review of the specimens from 102 biopsies failed to show sufficient evidence of a significant association between methotrexate, when administered on an intermittent basis, and hepatic fibrosis to justify continued routine liver biopsies in this institution. If the abnormalities that are of major concern, i.e., fibrosis and cirrhosis, occur gradually and are slowly progressive, a careful study of the changes seen in our biopsies,

TABLE IV

Grading of liver biopsies in patients with previous methotrexate therapy (treated) and no to minimal alcohol intake

Case	Age at biopsy	Total dose (mg)	Schedule*	Duration of Rx(years)	BSP	Hyperploid nuclei	Fat	Inflammation	Fibrosis	Necrosis
36	30	525	I	0.5	1.6	0	0	1	0	0
37	58	5000	C/I	8	n.d.	6	0	3	9	4
38	38	650	I	0.5	3.6	1	0	1	1	0
39	67	5000	C	5	7.8	3	2	4	4	0
40	31	1875	I	1.5	4.3	1	0	1	0	0
41	57	1125	C	2.5	12.9	6	0	13	16	7
42	54	3125	I	3.5	n.d.	3	0	2	1	0
43	33	3000	C/I	4.0	2.6	0	4	1	0	0
44	28	3000	I	3.0	2.7	0	4	1	0	0
45	56	960	C	4.0	4.3	2	1	0	0	0
46	22	2275	C	3.0	5.6	5	0	5	6	0
47	24	532	I	0.5	n.d.	0	0	1	1	0
48	54	1250	C	2.0	5.4	4	1	1	0	0
49	42	n.a.	n.a.	n.a.	1.1	2	0	3	3	1
50	27	2000	C	5.0	3.0	2	0	0	0	1
51	48	3000	C	5.0	7.5	8	5	4	2	0

*I = intermittent; C = continuous; n.d. = not done; n.a. = not available

TABLE V

Grading of liver biopsies in patients with previous methotrexate therapy (treated) and moderate to excessive alcohol intake

Case	Age at biopsy	Total dose (mg)	Schedule*	Duration of Rx(years)	BSP	Hyperploid nuclei	Fat	Inflammation	Fibrosis	Necrosis
52	58	1250	I	3.0	n.d.	1	4	1	3	0
53	64	5000	I	4.0	n.d.	8	0	3	2	0
54	42	225	I	0.5	14.2	1	12	3	2	1
55	48	1950	I	3.0	5.0	1	0	3	0	0
56	35	3750	I	3.0	n.d.	7	0	4	0	0
57	39	1440	I	1.5	3.5	2	9	1	0	0
58	38	480	I	0.5	6.6	0	5	2	1	0
59	40	2500	I	3.0	n.d.	0	0	0	0	0
60	34	n.a.	n.a.	3.0	2.9	4	3	7	4	1
61	58	100	C	0.3	7.0	1	11	4	4	1
62	40	2000	C	3.0	2.3	3	5	3	3	1
63	69	3200	C	5.0	9.7	4	7	2	2	1
64	48	2000	I	6.0	3.5	6	8	6	2	0
65	48	1875	C	2.0	5.5	4	6	6	3	1
66	61	792	I	1.0	8.3	0	6	4	0	2
67	25	2530	C	5.0	3.8	1	10	2	1	0
68	37	1680	C	3.0	n.d.	6	4	8	10	2
69	29	3750	C	6.0	3.0	4	4	5	0	0
70	37	640	C	1.0	3.0	4	6	6	6	1

* I = intermittent; C = continuous; n.d. = not done; n.a. = not available

which were numerically graded, should have allowed us to confirm this possibility.

A retrospective analysis of the initial liver biopsy of the 70 patients showed no significant differences in the histologic changes between the treated and untreated patients. The total scores for each histologic parameter of all four observers were used in the multivariate analysis of these data, thus eliminating any distortion of trends produced by classifying histologic changes into nondiagnostic and significant abnormalities. Of particular importance was the finding that the 32 repeat liver biopsy specimens in 21 patients showed no progression of any of these changes.

There remains the alternate possibility that the development of cirrhosis from methotrexate occurs only infrequently and/or is the result of rapid, massive, catastrophic morphologic change which will only be found by monitoring patients with frequent serial liver biopsies. However, on the basis of our findings, a prospective study in which it would be necessary to perform approximately 600 additional liver biopsies would be required to confirm statistically the low incidence of cirrhosis observed in the series.

The findings of the international cooperative study [15] have reconfirmed our decision to discontinue a protocol of routine repeat liver biopsies. In their analysis of 200 pre-methotrexate patients, the incidence of cirrhosis was 1.5% and in 372 post-methotrexate patients it was 2.7%. They concluded that the incidence of cirrhosis in the patients was no greater than the incidence of cirrhosis in a large combined series of 56,799 consecutive hospital autopsy examinations (3.04%). In addition, 81 patients in their series who had two sequential biopsies while continuing to receive methotrexate showed no progression of fibrosis.

Of special interest is the high incidence of apparently abnormal but nondiagnostic changes seen in the liver biopsy specimens of patients with psoriasis. In the 35 untreated patients, these nondiagnostic changes were seen in 80% of the biopsies. In addition, 71.4% of the treated cases showed similar changes. It should be emphasized that the incidence of such changes in a series of normal control needle liver biopsy specimens is not known nor is it likely that it will be determined in the near future. Such data would not justify the risks associated with performing liver biopsies in normal control subjects which would be necessary to obtain such information. The arbitrary classification of nondiagnostic and significant abnormalities used in the course of this study were necessary for the routine management of our patients before the statistical analysis was completed. Thus, the significance of the nondiagnostic changes remains unknown.

Our analysis of the schedule of methotrexate administration was limited by the small number of patients in the study. As methotrexate was administered only intermittently after the initial biopsy in the prospective portion of this study, our interpretation of the indications for liver biopsies refers only to methotrexate administered by an intermittent schedule.

The role of alcohol in the production of hepatic fibrosis in methotrexate-treated patients remains unclear. The lack of correlation of liver changes in our series in the methotrexate-plus-alcohol group

of subjects may be due to the small number of patients, to the difficulty in obtaining an accurate history of alcohol intake from the patients, or to the fact that some individuals did indeed discontinue alcohol intake before their liver biopsy. The series of Dahl et al [10] and Roenigk et al [8] have indicated that alcohol is not a necessary prerequisite to the development of significant hepatic abnormalities from methotrexate. Case #41 (Table IV) represents our only experience with cirrhosis. This patient was not under our care until the process was present. Nevertheless this case as well as the others in the literature speak strongly for the ability of methotrexate to cause cirrhosis in the absence of alcohol ingestion.

Weinstein et al [7] pointed out the need to distinguish between portal or micronodular cirrhosis and postnecrotic or macronodular cirrhosis. Many hepatologists feel that the hepatic injury resulting from alcohol may eventuate, in some cases, in macronodular cirrhosis [19], thus eliminating the validity for the distinction between these two types of cirrhosis in assessing the role of methotrexate in producing one form of cirrhosis. While it seems reasonable to assume that the adverse effect of alcohol on the liver may be synergistic with the potential hepatotoxic action of methotrexate, more data are needed. It may well be that these two agents are hepatotoxic by different and nonsynergistic mechanisms. It is also clear that fibrosis and even cirrhosis can be present in the absence of abnormal liver function tests [15]. Even BSP retention as a sensitive test of liver function has been discarded in a recent series [20]. Case #25 in this series illustrates this problem. Significant fibrosis was seen in the liver biopsy specimen in spite of normal liver function tests including the BSP retention. Although the question as to whether a liver biopsy prior to methotrexate therapy is necessary in order to avoid treating a patient with fibrosis cannot be answered at this time, it is of interest that when case #25 eliminated the ingestion of all alcohol, the degree of fibrosis improved markedly in spite of the administration of methotrexate on an intermittent-dosage schedule.

The morbidity resulting from liver biopsy has been virtually ignored in all studies to date dealing with the effect of methotrexate on the liver. The incidence of significant post-biopsy bleeding from a needle biopsy of the liver in this medical center is approximately 0.5%, or 1 in 200. While no fatalities have occurred in this Center as a result of this procedure, a laparotomy was necessary to control bleeding in the one major complication encountered in this study.

Having weighed the risk of liver biopsy against the information to be gained from routine prospective liver biopsies before methotrexate therapy, we find the need for such a procedure to be questionable at this time. Until there are long-term data available regarding the incidence of hepatic fibrosis from intermittent methotrexate administration from a large series of patients, the indications for liver biopsy in each case should be individualized to those patients in whom past or present liver disease is suspected.

Note added in proof

Since this study was completed one additional liver biopsy was performed. The procedure resulted in a significant postbiopsy bleed which fortunately was controlled without the necessity for a laparotomy.

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